Remarks

I. Support for Amendments

Support for the foregoing amendments to the claims may be found throughout the specification as originally filed, either inherently or explicitly. Specifically, support for the amendments to claims 50, 51, 54, 57 and 58 can be found in the specification at pages 8-9, 17-19, 36-37, throughout the Examples, and in claims 1, 2, 8, 10-12, 17-18, 26, 41, 43, 45 and 46 as originally filed. Hence, the foregoing amendments to the claims do not add new matter, and their entry into the present application is respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 50, 51, 54, 57 and 58 are sought to be amended. These amendments do not add new matter. Upon entry of the foregoing amendments, claims 50-58 are pending in the application, with claims 50 and 57 being the independent claims.

III. The Claimed Invention

The invention as presently claimed is drawn to compositions comprising an ordered and repetitive antigen or antigenic determinant array. Compositions of the invention may comprise, for example, a molecular scaffold comprising a virus-like particle linked via an organizer polypeptide (or residue thereof) to an antigen or antigenic determinant to form an ordered and repetitive antigen array. Among other applications, the compositions of the invention are useful in the production of vaccines for the treatment of infectious diseases, in the treatment of allergies, and as pharmaccines to prevent or cure cancer and to generate defined self-specific antibodies.

IV. Summary of the Office Action

In the Office Action dated February 27, 2002, the Examiner has made three rejections of the claims. Applicants respectfully offer the following remarks to overcome or traverse each element of this rejection in the Office Action.

V. The Rejection Under 35 U.S.C. § 112, Second Paragraph, Is Traversed

In the Office Action at pages 2-3, the Examiner has rejected claims 50-58 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection, in view of the following remarks.

A. The Recitation of "Non-Naturally Occurring Molecular Scaffold"

In making this rejection, the Examiner first contends that claim 50 is indefinite for reciting a "non-naturally occurring molecular scaffold," and has further noted that this claim "does not explicitly state that the organizer is not a naturally occurring component of the core particle." *See* Office Action at page 3, second paragraph. Applicants respectfully traverse this portion of the rejection.

Applicants first note that a definition for, and the construction of, a "non-natural molecular scaffold" is provided in significant detail throughout the specification as filed, particularly at pages 14 and 19-27, and throughout the Examples. To this end, the design and construction of exemplary (but non-limiting) non-natural molecular scaffolds are described in Examples 21 and 23, while the subsequent association of antigens to the designed non-natural molecular scaffolds is described in Examples 22 and 25. The design of a non-natural molecular scaffold, and thus, the formation of the exemplary ordered and repetitive antigen array of Example 25, involved the development of a tailored (*i.e.*, "non-natural") organizer that is not a naturally occurring component of the virus-like particle core, which in this example was the peptide Gly-Gly-Lys-Gly-Gly. Prior to the connection of the organizer to the virus-like particle core (in this example, the HBcAg), the subunits of the virus-like particle core were adapted to the tailored organizer by deleting two amino acids of their tip region leading to the "HBcAg-Lys" construct. The connection of the organizer and the virus-like particle core within this particular example was effected by way of genetic engineering as indicated in Example 23. Hence, in the embodiment of the invention exemplified in non-

limiting Examples 23-25, the organizer is not a naturally occurring component of the virus-like particle core.

However, Applicants note that one of ordinary skill would immediately recognize that the definitions of "organizer" and "core particle" in the present specification also provide for situations in which the organizer is a part of the virus-like particle. Hence, although the molecular scaffold of the claimed conjugates is non-natural, the organizer itself need not be. Indeed, non-natural molecular scaffolds can be assembled from natural or non-natural virus-like particles in combination with natural or non-natural organizers, as the present specification clearly teaches (*see, e.g.*, Specification at page 12, lines 13-16; at page 14, lines 13-24; at page 15, lines 4-13; at page 18, lines 1-5; and at pages 19-27). The statement in Applicants' previous response (and referred to by the Examiner in the present Office Action) -- that an important feature of the conjugates is that the organizer is not a naturally occurring part of the core (virus-like) particle -- was made with reference *solely* to the embodiments specifically exemplified in Examples 23-25 of the specification (which were the subject of discussion in the section of the response referred to by the Examiner), and was not intended to refer to *all* conjugates encompassed within the claimed invention. Hence, it is not correct to state that non-natural molecular scaffolds *a priori* have non-natural organizers; the present specification provides support for non-natural molecular scaffolds constructed of natural and non-natural virus-like core particles, and natural and non-natural organizers. All that is necessary is that the scaffold itself be non-natural (*i.e.*, a "product of the hand of man," as that term is defined in the present specification).

To clarify this situation, but not in acquiescence to this portion of the rejection, claim 50 has been amended to explicitly recite a "non-natural molecular scaffold." Reconsideration and withdrawal of this portion of the rejection under 35 U.S.C. § 112, second paragraph, are therefore respectfully requested.

B. The Recitation of "Core Particle" and "Virus-Like Particle"

The Examiner next contends that claim 50 is indefinite for reciting both a "core particle" and a "virus-like particle." Specifically, the Examiner contends that since for certain viruses, there is a distinction between core particles and virus-like particles, "[i]t is not clear if the intent is any virus-like particle or more narrowly a core-like particle." Paper No. 18 at page 2, third paragraph. Applicants respectfully disagree with these contentions.

The definition of a "core particle" provided in the specification clearly indicates that this term is to be understood in its generic sense:

> As used herein, the term "core particle" refers to a rigid structure with an inherent repetitive organization that provides a foundation for attachment of an "organizer." A core particle as used herein may be the product of a synthetic process or the product of a biological process.

Specification at page 12, lines 13-16. Hence, as used in the present specification and in claim 50, the term "core particle" does not refer to a viral core protein *a priori*. Instead, as one of ordinary skill would readily understand from the context in which this term is used throughout the specification, the "core particle" simply is the underlying foundation of the molecular scaffold -- *i.e.*, the base structure upon which the remainder of the scaffold (and

hence, the ordered and repetitive antigen arrays of the invention) is built. As such, the term "core particle" is used more broadly in the present claims than the Examiner has apparently construed this term. Nonetheless, to provide additional clarity to this recitation, and not in acquiescence to this portion of the rejection, claims 50 and 57 (and the claims depending therefrom) have been amended to delete recitation of the "core particle" and to recite a "virus-like particle." Thus, this portion of the rejection has been accommodated; reconsideration and withdrawal are therefore respectfully requested.

C. The Recitation of "Vaccine Composition"

The Examiner next contends that claims 57 and 58 are indefinite since they appear to be duplicates of claims 50 and 51 with the exception of the preamble. By the foregoing amendments, claim 57 has been amended to include recitation of "a pharmaceutcially acceptable carrier." Applicants respectfully assert that by this recitation, it is clear that claims 57 and 58 are intended to encompass compositions comprising the conjugates of the invention in a suitable carrier, for use as a vaccine composition. Thus, this portion of the rejection has been accommodated; reconsideration and withdrawal are therefore respectfully requested.

D. Summary

In view of the foregoing remarks, Applicants respectfully assert that the present claims particularly point out and distinctly claim the subject matter regarded by Applicants as the

invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, are therefore respectfully requested.

VI. The Rejection Under 35 U.S.C. § 112, First Paragraph, Is Traversed

In the Office Action at page 3, the Examiner has rejected claims 57 and 58 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that "[t]he specification provides teachings on making virus-like particles with attached antigens, but provides no teachings on inducing an immune response sufficient to prevent disease." Paper No. 18 at page 3, lines 11-13. Applicants respectfully disagree.

Applicants note that claim 57 is drawn to "a vaccine composition," which by definition is an immunogenic composition, which the Examiner has acknowledged is fully enabled by the present specification. *See* Paper No. 18 at page 3, lines 7-8. The Examiner's point appears to be that to be entitled to a claim for "a vaccine composition," the specification must teach the use of such a composition in vaccinating against *any* disease. This point is factually and legally unsupportable.

First, as the present specification amply teaches and as one of ordinary skill would readily recognize, viruses and immunogens based on viruses (or virus-like particles) are well-known in the art for their value in vaccines against a variety of diseases and disorders. As is understood by those of ordinary skill, the value of a vaccine composition depends upon the

particular antigens that are present within that composition; a vaccine against malaria, for instance, would contain malarial antigens or haptens, while a vaccine against influenza would contain influenzavirus antigens or haptens. Thus, a claim drawn to a "vaccine composition" *per se* need not specifically indicate the particular disease it is directed against, unless it also recites the particular antigens that are contained in that vaccine. The presently claimed vaccine compositions are drawn more broadly, since the point of the compositions is the *presentation* of the antigenic determinants, not their *identity*. Hence, since one of ordinary skill would immediately recognize based on the teachings of the present specification that the presentation of *any* antigenic determinant in an ordered, repetitive way would lead to an immunogenic response in an animal immunized with such a composition, the present specification fully enables claims of this scope.

Second, the present specification provides ample detail that would enable one of ordinary skill to prepare vaccine compositions comprising any antigen. For example, at pages 28-29, the specification clearly teaches the use of antigens or antigenic determinants permitting the construction of vaccines for treating a variety of infectious diseases, including but not limited to viral diseases; bacterial diseases, parasitic diseases; allergic disorders; cancers; and the like. Since vaccine compositions for treating such diseases and disorders are well-known in the art, one of ordinary skill would not find it unreasonable that the present vaccine compositions, using such antigens, would be useful for therapeutic purposes.

Finally, the present specification clearly teaches the use of such compositions and vaccines in the treatment of a variety of diseases and disorders. For example, at pages 35-37,

the specification teaches the use of the vaccine compositions of the present invention in treating diseases and disorders such as those described above, in a variety of animals. Again, since the use of vaccine compositions in the treatment and prevention of diseases and disorders is well-known in the art, one of ordinary skill would have no reason to doubt that the compositions of the present invention, which are immunogenic as acknowledged by the Examiner, would be useful as vaccine compositions.

Applicants remind the Examiner that the enablement requirement of 35 USC § 112, first paragraph, is satisfied if the claimed invention is enabled so that any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In order to establish a *prima facie* case of non-enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original). As discussed above, Applicants submit that the claimed vaccine compositions could be made and used by those of ordinary skill in the art without undue experimentation. Additionally, Applicants respectfully assert a sufficient explanation or sound scientific reasoning as to why the

specification would not enable the claimed invention has not been provided. Hence, a *prima facie* case of non-enablement has not been established.

As the Federal Circuit has held:

> [t]he purpose of [the enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and knowledge in the art.

Scripps Clinic & Research Foundation v. Genentech, Inc., 18 USPQ2d 1001, 1006 (Fed. Cir. 1991). Therefore, the Examiner is respectfully reminded that the proper standard of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the application, coupled with information known in the art, without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 107 S. Ct. 1606 (1987). It is requested that in reconsidering this rejection, the Examiner also keep in mind that the question of undue experimentation is a matter of degree, and "the key word is 'undue,' not 'experimentation.'" *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), quoting *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation must not be unduly extensive. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), citing *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir.1984). To demonstrate the efficacy of a given vaccine composition such as those of the present invention, one of ordinary

skill would be prepared to screen candidate vaccines for their ability to induce an immune response, using *in vitro* and *in vivo* methods that have been well-known in the art for many years. Indeed, practitioners in the vaccine arts routinely undertake such screening and optimization experimentation without considering it undue. *Cf. Wands*, 8 USPQ2d at 1406. Furthermore, the test of whether an amount of experimentation is undue is not merely quantitative; a considerable amount of experimentation is permissible, if it is merely routine (*i.e.*, uses methods known to those of ordinary skill in the relevant arts), or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *See PPG Indus.*, 37 USPQ2d at 1623, citing *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. & Inter. 1982). Since the present specification provides significant guidance on how to make and use vaccine compositions comprising a variety of antigens and antigenic determinants, Applicants respectfully assert that one of ordinary skill could readily make and used the claimed vaccine compositions without the need for undue experimentation.

Applicants also remind the Examiner that in order to enable a claimed invention, a specification need not teach, and preferably omits, information that is well-known to those of ordinary skill in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1463 (Fed. Cir. 1984); *Wands*, 8 USPQ2d at 1402. In addition, one of ordinary skill in the art is deemed to know not only what is considered well-known, but also where to search

for any needed starting materials. *See In re Howarth*, 210 USPQ 689, 692, (CCPA 1981). As noted above, methods for screening candidate vaccines for their abilities to induce an immune response are well-known in the art. In addition, the structures of and methods for preparing a variety of candidate vaccine conjugates are taught in detail in the present specification, and such conjugates are acknowledged by the Examiner to be immunogenic. The present specification also clearly describes methods for use of the present vaccine compositions in treating and preventing a variety of diseases and disorders. Therefore, in view of the teachings of the present specification and information that is known in the art (which, under *Hybritech*, *Lindemann Maschinenfabrik*, *Wands*, and *Howarth*, need not be taught in, and preferably is omitted from, the present specification), one of ordinary skill would be able to make and use the compositions of claims 57 and 58 with a reasonable expectation of success and without undue experimentation. Under *Marzocchi* and *Wands*, the specification therefore must be taken as enabling the full scope of the claimed compositions, since no objective evidence or sound scientific reasoning has been provided to question this scope of enablement.

In view of the foregoing remarks, Applicants respectfully assert that the specification fully enables the present invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, therefore are respectfully requested.

VII. The Rejection Under 35 U.S.C. § 102(e) Is Traversed

In the Office Action at pages 4-5, the Examiner has rejected claims 50, 51, 54, 57 and 58 under 35 U.S.C. § 102(e) as being anticipated by Birkett, U.S. Patent No. 6,231,864 (Doc. No. A1 on the Form PTO-892 attached to Paper No. 18; hereinafter "Birkett"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that Birkett discloses each limitation of the presently claimed invention. Applicants respectfully disagree. Specifically, Applicants note that Birkett does not disclose the formation of "an ordered and repetitive antigen array" through the interaction of an antigenic determinant and a non-natural molecular scaffold. In Birkett, haptens are coupled to hepatitis B core antigens via chemical cross-linking to reactive amino acid residues (*e.g.*, Lys, Cys, His, Asp or Glu, and particularly Lys) that have been engineered into the viral core antigen (*see* Birkett, abstract, and at cols. 4, 10-12, 25-26 and 28-29). Haptens are then coupled to such reactive residues in a random fashion, using chemical cross-linking (*see* Birkett, abstract, and at cols. 13-22 and 26-27, *e.g.* at col. 13, lines 49-54). These processes result in multiple coupling events occurring between multiple haptens and a single engineered viral capsid protein, since the coupling processes are random and are not controlled as they are for the present invention, where the antigen or antigenic determinant and the non-natural molecular scaffold are brought together through this association of the first and the second attachment site to form an ordered and repetitive antigen array (*see* present specification at page 18, line 12-15).

In Example 4, Birkett states that approximately 50 percent of the strategically modified HBc monomers were operatively linked to hapten, whereas only 5 percent of the "wild type" HBc particles were linked to hapten. *See* Birkett at col. 27, lines 44-47. Birkett, thereby, refers to the increased coupling efficiency of hapten to the strategically modified HBc. *See* Birkett at col. 3, line 60 to col. 4, line, 2.

Importantly, however, Birkett indicates in Example 4 that no more than 50% of the strategically modified HBc monomers were successfully coupled to a hapten. *See* Birkett at col. 28, lines 5-8. Birkett refers to the presentation of hapten on the ends of "spikes" (as does the Examiner), which is due to the relatively exposed immunodominant loop regions of the core, and states that 50% conjugation "corresponds to an average of one hapten attached per core particle spike." *See* Birkett at col. 28, lines 1-10. However, it must be emphasized that the close spatial arrangement of the "spikes" caused by the relatively exposed immunodominant loop regions of the core in Birkett does not indicate that the haptens are displayed in an ordered and repetitive array. Instead, this result only indicates that even at this "average" distribution, the propensity for steric constraints are minimized due to the strategic location of the introduced insert. *See* Birkett at col. 27, line 63 to col. 28, line 5.

Hence, the methods of Birkett result in the production of particles in which antigens are presented in a random, non-ordered fashion. As the present specification amply points out, and as one of ordinary skill would be well-aware, such a random presentation of antigen is a significant disadvantage in the development of vaccine compositions:

> [a]ntigens coupled to a surface in a random orientation are found to induce CTL response

> and no or only weak B-cell response. For an efficient vaccine, both arms of the immune system have to be strongly activated . . . .

Specification at page 6, lines 6-8. The conjugates and compositions of the present invention provide for the presentation of antigenic determinants in a highly ordered molecular array, and thereby overcome the limitations of art-known compositions where the antigen is presented in a random fashion.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). Since Birkett does not disclose the production of conjugates or compositions in which an antigen is presented in an ordered and repetitive antigen array, this reference cannot and does not anticipate the present invention. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) over Birkett be reconsidered and withdrawn.

VIII. Other Matters

Applicants acknowledge the Examiner's statement at page 5 of the Office Action that claims 52, 53, 55 and 56 remain free of the prior art. In view of the foregoing remarks, Applicants respectfully assert that all of the pending claims are in condition for immediate allowance. Early notification to this effect is solicited.

IX. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding rejections.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt entry and favorable consideration of the foregoing amendments and remarks, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

Claims 50, 51, 54, 57 and 58 are amended as follows:

50. (Once amended) A composition comprising:

(a) a [non-naturally occurring] non-natural molecular scaffold comprising:

(i) [a core particle, wherein said core particle is] a virus-like particle; and

(ii) an organizer comprising at least one first attachment site,

wherein said organizer is a polypeptide or residue thereof and is connected to said [core] virus-like particle by at least one covalent bond; and

(b) an antigen or antigenic determinant with at least one second attachment site, said second attachment site being selected from the group consisting of:

(i) an attachment site not naturally occurring with said antigen or antigenic determinant; and

(ii) an attachment site naturally occurring with said antigen or antigenic determinant,

wherein said second attachment site is a polypeptide or residue thereof and is bound by at least one non-peptide bond to said first attachment site; [and]

wherein said antigen or antigenic determinant and said scaffold interact through said association to form an ordered and repetitive antigen array.

51. (Once amended) The composition of claim 50, wherein said [core] virus-like particle is a hepatitis B virus capsid protein.

54. (Once amended) The composition of claim 50, wherein said [core] virus-like particle is selected from the group consisting of:

(a) recombinant proteins of Rotavirus;

(b) recombinant proteins of Norwalk virus;

(c) recombinant proteins of Alphavirus;

(d) recombinant proteins of Foot and Mouth Disease virus;

(e) recombinant proteins of Retrovirus;

(f) recombinant proteins of Hepatitis B virus;

(g) recombinant proteins of Tobacco mosaic virus;

(h) recombinant proteins of Flock House Virus; and

(i) recombinant proteins of human Papillomavirus.

57. (Once amended) A vaccine composition comprising:

(a) a [non-naturally occurring] non-natural molecular scaffold comprising:

(i) [a core particle, wherein said core particle is] a virus-like particle; and

(ii) an organizer comprising at least one first attachment site,

wherein said organizer is a polypeptide or residue thereof and is connected to said [core] virus-like particle by at least one covalent bond; [and]

(b) an antigen or antigenic determinant with at least one second attachment site, said second attachment site being selected from the group consisting of:

(i) an attachment site not naturally occurring with said antigen or antigenic determinant; and

(ii) an attachment site naturally occurring with said antigen or antigenic determinant,

wherein said second attachment site is a polypeptide or residue thereof and is bound by at least one non-peptide bond to said first attachment site; [and]

wherein said antigen or antigenic determinant and said scaffold interact through said association to form an ordered and repetitive antigen array; and

(c) a pharmaceutically acceptable carrier.

58. (Once amended) The vaccine composition of claim 57, wherein said [core] virus-like particle comprises a Hepatitis B virus-like particle.